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Evaluation of Risk Factors and Clinical Outcome Related To ESBL-Producing *E.coli* Infection among Hospitalized Patients

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Abstract:
Introduction: *Over decades, infections caused by extended-spectrum β-lactamase (ESBL)-producing Escherichia coli have become a major problem all around the world. This situation is of concern because there are limited antimicrobial options to treat patients infected with these pathogens, and also because this kind of resistance can spread to a wide variety of Gram-negative bacilli. Our objectives are thus to evaluate among in-patients at a tertiary-care hospital with documented infection due to E.coli, which were the risk factors and the clinical impact associated with an ESBL-producing strain in a prospective case control design.*
Methodology: *Eighty five patients admitted to Shri Mahant Indresh Hospital (SMIH) with invasive infections from ESBL –E.coli were employed as cases. Patients admitted to SMIH with non-ESBL producing E. coli invasive infection were chosen as controls.*
Results: *In univariate analysis,the following factors were found significant for ESBL-E.coli:Pre-infection hospital stay,recent stay,recent surgery,previous hospitalization and previous antibiotic use.Also ESBL producing E. coli were associated with longer duration of hospital stay,greater hospital charges and had significant impact on clinical outcome.*
Conclusion: *Efforts need to be taken to control outbreaks of infection with ESBL producing E. coli which include judicious use of antibiotics and barrier precautions.*
Keywords: *ESBL, risk factors, case control study, clinical outcome*.

I. Introduction

In Gram negative pathogens, β-lactamase production remains the most important contributing factor to β-lactam resistance. This resistance is chiefly due to plasmid mediated extended spectrum β-lactamase (ESBL) production. They can be found in a variety of Enterobacteriaceae species; however, the majority of ESBL producing strains belong to genus Klebsiella and Escherichia. Resistance by virtue of production of ESBL in gram negative bacteria is an emerging problem leading to therapeutic failure when β-lactam drugs are used(1,2).

Studies from various countries indicate that the major risk factors for acquisition of ESBL-producing Enterobacteriaceae include severity of illness, length of hospital stay, invasive procedures, intravascular devices, haemodialysis, decubitus ulcers, poor nutritional status ,administration of total parenteral nutrition, low birth weight, antibacterial administration (Extended spectrum cephalosporins) Aztreonam, Fluoroquinolones, Cotrimoxazole, Aminoglycosides and Metronidazole (3-8). Reservoirs/vectors include healthcare worker hand colonization, contaminated ultrasonography gel, thermometers and cockroaches (9,10). It has also been demonstrated that this kind of infection increases length of stay among hospitalized patients producing a significant economic impact. Even though risk factors for acquisition of ESBL-producing organisms have been reported , data from this part of North India are not sufficient. This study aims to assess the risk factors and clinical impact associated with ESBL-producing strains, compared to non-ESBL-producing strains among in-patients at a tertiary care hospital with documented infection caused by *E.coli* spp.

II. Materials And Methods

Study location:

The study was performed at Shri Mahant Indresh Hospital and Shri Guru Ram Rai Institute of Health and Medical Sciences situated in Dehradun city.It is one of the teaching hospitals in North India.

Study population:

Cases and Controls: The research project was submitted to the Local Ethics Committee and was approved. Between January 2012 and August 2012, we investigated every strain of *E coli* isolated in the microbiology laboratory of the study hospital in order to identify potential eligible patients.Only patients with signs and symptoms of active infection were included in the study. Patients were excluded if they had a documented infection with an ESBL-producing organism previous to the study period.Controls consisted of the patients admitted to the hospital during the same period and from whom E.coli that were not ESBL-producing were

recovered.One patient was selected as a control for each case patient;the following suitable patient after identification of each case was included as control.

Clinical data were collected from the medical records and also from physical examination of the patients. Demographic and clinical data like sex, age, date of admission, date of infection diagnosis, pre-infection hospital stay, nosocomial origin and date of discharge were collected.The diagnosis of nososcomial infection was established according to CDC criteria(11).

Co-morbid conditions :renal diseases, hepatic dysfunction, malignancy, diabetes, neutropenia, HIV infection, prior organ transplant, steroid use ,surgical intervention or any traumatic injury in the past 30 days prior to admission,presence of devices and admission to ICU were examined.

The relationship between ESBL- producing E.coli strains and the use of antibiotic was assessed. The antibiotic were grouped as Carbapenems, Third generation Cephalosporins, Quinolones, Aminoglycosides, Cotrimoxazole and others. Previous antibiotic therapy was defined as any systemic antibiotic given for at least seven days within 30 days preceding the isolation of the organism.

Role of ESBL-resistance in outcomes Clinical and Microbiological outcomes were assessed.

Clinical outcome was classified as follows; "complete response," for patients who had resolution of fever,leukocytosis, and all signs of infection; "partial response," for patients who had abatement of abnormalities in the above parameters without complete resolution; " failure," for patients who had absence of abatement or deterioration in any clinical parameters; and "uncertain," for patients who had intermittent or recurrent signs and symptoms that were not clearly attributable to infection. Microbiological outcome was classified as follows:"definite response, "for patients whose cultures were sterile after a course of antimicrobial therapy; "probable response," for patients whose cultures were sterile during a course of anti microbial therapy; "failure," for patients who had persistent isolation of the organism after atleast 3 days of antimicrobial therapy; and "uncertain," for patients who had intermittent isolation of the pathogen with no clear temporal association with antimicrobial therapy or absence of subsequent cultures to assess microbiological response(12,13).

Microbiological methods:

The bacterial strains were identified using the standard microbiological techniques.Susceptibility to antimicrobial agents was determined using disk-diffusion susceptibility testing, according to the criteria of the Clinical Laboratory Standards Institute(14) .

All isolates of E.coli spp. were submitted to ESBL detection tests with ceftazidime and cefotaxime, each alone or combined with clavulanic acid, in order to obtain a more sensitive detection Strains were considered to be ESBL-producers when they tested positive in at least one detection test. K. pneumoniae ATCC 700603 was used as a positive control and E. coli ATCC 25922 as a negative control for the ESBL detection tests(14).

Statistical analysis:

The relation between ESBL-producing E.coli strains and possible risks factors was evaluated.All information were tabulated in a data base using the GraphPad Instat 3 software.The Chi- square test and the independent samples t test were used for categorical and continuous variables,respectively.Odds ratios(OR) and their 95% confidence intervals (CI) were calculated from 2-by-2 contigency tables. A p- value of<0.01 was considered significant. In addition,the relation between ESBL producing E.coli and the use of antibiotic groups as well as clinical outcome was also assessed.

III. Results

Study sample

During the study period ,a total 85 ESBL producing E.coli were obtained from hospitalised patients.These 85 patients were included in the study as cases.Controls were identified consecutively on a 1:1 ratio to the cases and were matched on the date of isolation of E.coli ;therefore,the final cohort consisted of 170 patients(85 cases and 85 controls)

Maximum samples were received from Surgery wards (Neurosurgery, Plastic Surgery etc.) (29.4%) followed by ICUs (21.9%) and Nephrology (17.6%).Also maximum E.coli ESBL isolates were obtained from Urine sample(74.0%) followed by Pus sample(14.6%).

The duration of hospitalization was 22.11(± 20.11) days in all patients. The mean duration of hospitalization in the case group was 40.22 (± 20.26) days and 14.0(± 7.4) days (P<0.01) in controls.

Case and control patients were of same age and had a slightly female predominance.(Table 1).Case patients were more likely to have had longer pre-infection hospital stay, recent surgery,previous hospitalization and previous antibiotic use than were controls(Table 1).

When co-morbid conditions of the two groups were compared,case patients were significantly more likely than were control patients to have renal diseases and diabetes.Malignancy and traumatic injury were more

common in case patients than they were among control patients,although the differences were not statistically significant(Table 2).

Finally,case patients had greater exposure to carbepenems, third generation cephalosporins, quinolones, aminoglycosides, cotrimoxazole and other antibiotics than the control patients.When the antibiotic groups were compared using the Chi-square test,the most significant antibiotic group for ESBL-production was quinolones(Table 3).

Results of antibiotic susceptibility testing for the 85 ESBL producing E.coli isolates to non-beta lactam antibiotics are shown in Figure 1.Polymyxin B and Tigecycline were the most effective antibiotics.

Of the case patients,64 (75.55%)had complete or partial clinical response to therapy compared with 71(83.52%) of control patients.When microbiological outcomes were compared, case patients 49(57.74%) and control patients 28(32.93%)had complete or partial response to therapy(Table 4).

Table :1

Characteristic	Case(n=85)	Controls(n=85)	OR(95% CI)	P value
Age, median y	32	33	0.97(0.71-1.33)	0.876
Gender(male %)	40	41	0.97(0.72-1.32)	0.872
Pre-infection hospital stay(> 7 days)	59	31	2.01(1.40-2.86)	<0.01
Nosocomial origin	64	54	1.34(0.92-1.94)	0.137
Central Venous Catheter	61	58	1.08(0.77-1.51)	0.733
Urinary Catheter	56	57	0.97(0.71-1.33)	0.870
Recent Surgery	25	06	1.86(1.44-2.41)	<0.01
Admission to ICU	18	13	1.20(0.85-1.70)	0.425
Previous Hospitalization	26	05	1.97(1.54-2.53	<0.01
Previous antibiotic use	57	13	2.90 (2.08-4.06)	<0.01

Table :2

Comorbid condition	Case(n=85)	Controls(n=85)	OR(95% CI)	P value
Renal diseases	52	42	1.63(1.22-2.16)	<0.01
Hepatic dysfunction	05	09	0.67(0.32-1.38)	0.343
Malignancy	12	02	1.83(1.39-2.40)	0.012
Diabetes	44	05	2.65(2.03-3.45)	<0.01
Neutropenia	00	01	-	-
HIV Infection	00	00	-	-
Trauma	10	02	1.75(1.29-2.37)	0.036
Transplant	00	00	-	-
Steroid use	08	00	2.10(1.79-2.47)	0.011
CNS diseases	04	03	1.15(0.59-2.22)	0.699

Table:3

Antibiotics	Case(n=85)	Controls(n=85)	OR (95% CI)	P value
Carbapenems	13	2	1.15(0.77-1.71)	0.653
Third gen. Cephalosporins	15	6	1.52(1.10-2.09)	0.062
Quinolones	13	1	2.01(1.60-2.51)	<0.01
Aminoglycosides	03	4	0.85(0.35-2.03)	0.699
Cotrimoxazole	05	3	1.26(0.73-2.21)	0.717
Others	11	6	1.33(0.90-1.97)	0.306

Figure 1:

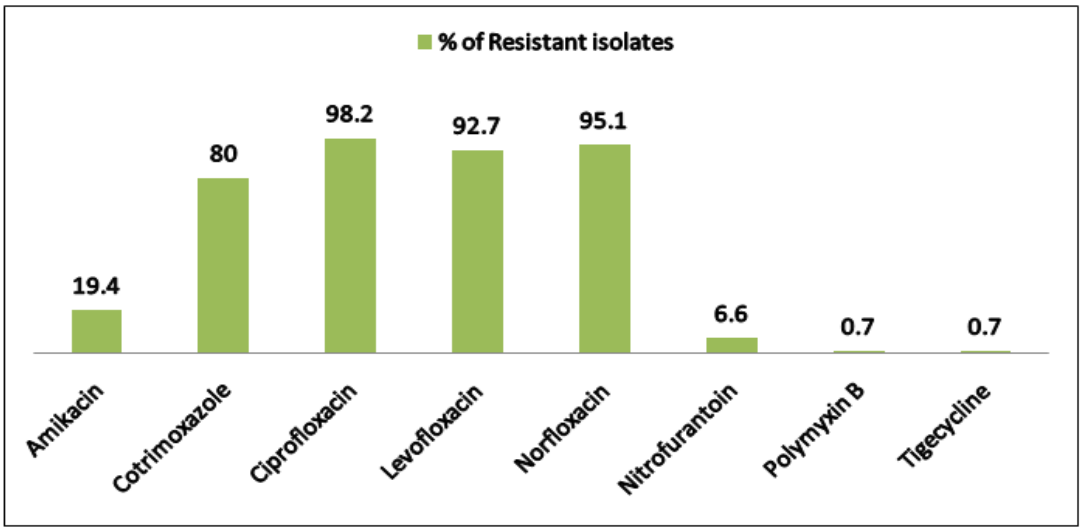

Table :4

Outcome	Case patients n (%)	Control patients n (%)
Clinical		
Complete response	41 (48.23)	63(74.11)
Partial	23(27.32)	08(09.41)
Failure	03(03.52)	03(03.52)
Uncertain	18(21.17)	12(14.11)
Microbiological		
Definite response	10(11.76)	04(04.70)
Probable response	39(45.88)	24(28.23)
Failure	0 (0)	03(03.52)
Uncertain	36(42.35)	54(63.52)

IV. Discussion

ESBL producing *E.coli* has emerged as an important cause of nosocomial and community acquired infections having limited therapeutic options.Presence of ESBLs compromises the activity of a wide spectrum of antibiotics creating major therapeutic difficulties with a significant impact on the outcome of the patients(15,16,17).

In the present study,we observed that ESBL burden was highest in surgery ward and various ICUs being (21.9%) and (17.6%) resp. Like our study Babypadmini et al. and Wani et al. have also detected majority of ESBL producers from ICU and surgical ward (18,19)

Infection with ESBL-producing *E.coli* was associated with a longer mean duration of hospital stay than the control groups.The mean duration of hospitalization for case patients was 2.87 times higher than the control groups which is consistent with studies by Shanthi and Sekar,2010.

Previous studies have shown that major risk factors related to ESBL-producing E. coli include:severe underlying disease,prior administration of multiple antibiotics,surgical intervention,presence of indwelling catheters,long stay in the hospital,intubation,mechanical ventilator assistance in intensive care and others(20-23).In our study we found pre-infection hospital stay,recent surgery,previous hospitalization and previous antibiotic use to be significant risk factors for acquisition of ESBL producing isolates.

The role of antibiotics use has been emphasized as the leading risk factor associated with ESBL producing organisms.The use of Third generation cephalosporins ,quinolones,aminoglycosides and carbepenems have seen to be associated with regard to increased number of cases of ESBL-producing organisms(8).Our results support that there is a significant association between previous antibiotic intake and infections due to ESBL-producing organisms.In our study,only fluroquinolones were found significant among the antibiotic classes. Amongst co-morbid conditions diabetes and malignancy were significantly associated with ESBL-E.coli.

ESBL producing E.coli may result in higher rates of treatment failure and death due to a delay in adequate antimicrobial therapy.Adequate,timely empirical antimicrobial therapy contributes to successful treatment of patients with ESBl-E.coli.Our study showed that both clinical as well as microbiological response after anti-microbial therapy was good amongst control group than cases which is consistent with study by Kutbettin et al.We found that infection with ESBL-producing E. coli were associated with significantly longer durations of hospital stay and thus increased hospital charges than were infections due to susceptible organisms.

V. Conclusion

We have demonstrated that pre-infection hospital stay, recent surgery, previous hospitalization and previous antibiotic use are major risk factors for acquiring infections with ESBL-producing organisms especially ESBL producing E.coli. To reduce the prevalence of antimicrobial resistant pathogens, including ESBL producing Enterobactericeae, effective infection control measures like hand washing and barrier precautions are required. Monitoring the judicious use of antibiotics, periodic surveillance of antibiotic resistance patterns and efforts to decrease empirical antibiotic therapy would go a long way in addressing some of the problems associated with these pathogens.

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